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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/70</b>	<b>A1</b>	(11) International Publication Number: <b>WO 98/17280</b> (43) International Publication Date: 30 April 1998 (30.04.98)
<p>(21) International Application Number: PCT/GB97/02862</p> <p>(22) International Filing Date: 17 October 1997 (17.10.97)</p> <p>(30) Priority Data: 9621771.6 18 October 1996 (18.10.96) GB 028,693 18 October 1996 (18.10.96) US</p> <p>(71) Applicant (for all designated States except US): ST. GEORGE'S ENTERPRISES LTD. [GB/GB]; St. George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE (GB).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): GUPTA, Sandeep [GB/GB]; 26 Broomfield Avenue, Palmers Green, London N13 4JN (GB).</p> <p>(74) Agents: MARSDEN, John, Christopher et al.; Frank B. Dehn &amp; Co., 179 Queen Victoria Street, London EC4V 4EL (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: METHOD OF TREATMENT OF HEART DISEASE CAUSED BY CHLAMYDIA PNEUMONIAE</p> <p>(57) Abstract</p> <p>A method of combatting atherosclerosis, said method comprising administering an effective amount of a macrolide antibiotic, for example an azalide such as azithromycin, optionally together with one or more pharmaceutically acceptable carriers or excipients, to a subject.</p>		

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## METHOD OF TREATMENT OF HEART DISEASE CAUSED BY CHLAMYDIA PNEUMONIAE

FIELD OF THE INVENTION

This invention relates to the treatment of heart disease, more particularly to the use of certain antibiotics in combatting atherosclerosis.

DESCRIPTION OF THE PRIOR ART

Coronary heart disease is the largest single cause of premature death in the western world, and in the UK alone is responsible for about 160,000 deaths annually. The traditional view held by a significant proportion of the medical profession is that age and social and economic factors are the predominant causes of heart disease. In recent years, however, there has been a significant number of reports implicating certain bacteria in coronary heart disease, although these have met with considerable scepticism in some quarters.

Bacteria referred to in such reports include *Helicobacter pylori* and *Chlamydia pneumoniae*. Thus, for example, Finnish researchers in the late 1980s reported that coronary heart disease sufferers were more likely to have high levels of antibodies to the *Chlamydia pneumoniae* bacterium than healthy people (The Lancet, 1988: 983-986). More recently, the organism itself has been found in atherosclerotic arteries of patients undergoing abdominal aortic aneurysm repair (J. Clin. Pathol., 1996, 49(2): 102-106). In the Journal of the American College of Cardiology, June 1996, 27(7): 1555-61, it was reported that 79% of patients undergoing surgery to excise atherosclerotic plaques showed an antibody to *Chlamydia pneumoniae* active in the lesions, but that only 4% of non-atherosclerotic pathology specimens showed the same antibody. It was alleged on this basis that the bacterium may be specifically linked with atheroma and not with other causes of arterial

damage.

Other workers have reported similar findings, and it has been suggested that inflammation associated with persistent bacterial infection of arterial walls could trigger an immune reaction which raises fibrinogen and tissue factor levels in the blood and increases the potential for atherothrombosis.

However, there is still considerable scepticism about this theory within the medical profession, particularly amongst cardiologists, and many workers doubt whether *Chlamydia pneumoniae* is present in the diseased heart at all or, if it is, it is merely there as an innocent bystander. Thus, in the Journal of Infectious Diseases, 1996, 173(4): 957-62 it was reported that a research team had failed to culture *Chlamydia pneumoniae* from 58 samples of atheroma. Opinions are therefore firmly divided on the role, if any, of *Chlamydia pneumoniae* in heart disease.

The present invention is based on the unexpected finding that administration of certain antibiotics, more specifically macrolide antibiotics such as azithromycin, may lead to a reduction in markers of blood clotting and inflammation in the blood of post-myocardial infarction patients, possibly through eradication of underlying *Chlamydia pneumoniae* infection. Such administration of macrolide antibiotics may therefore be beneficial not only to cardiac patients, for example by reducing inflammation of heart tissue, blood clotting, susceptibility to angina, the likelihood of re-admissions and/or need for bypass or other surgery, but also prophylactically to patients in general.

#### SUMMARY OF THE INVENTION

Thus viewed from one aspect the present invention provides a method of combatting atherosclerosis, said method comprising administering an effective amount of a macrolide antibiotic, for example an azalide, optionally together with one or more pharmaceutically acceptable

carriers or excipients, to a subject.

In the method according to the invention, the macrolide antibiotic may if desired be administered with other useful agents such as platelet aggregation inhibitors, blood thinning agents, and/or lipid lowering agents. Thus in a further aspect, the present invention provides a composition for combatting atherosclerosis, the composition comprising a macrolide antibiotic or a derivative thereof, e.g. azithromycin together with one or more of the agents selected from the group consisting of platelet aggregation inhibitors, blood thinners, and/or lipid-lowering agents etc, optionally together with one or more carriers or excipients.

Viewed from a further aspect the present invention provides the use of a macrolide antibiotic e.g. azithromycin or a derivative thereof for the preparation of a composition for use in combatting atherosclerosis.

As is well known, macrolide antibiotics are characterised by the presence of a macrocyclic lactone ring to which one or more sugar molecules are attached. Representative examples of such antibiotics include erythromycin, spiramycin, oleandomycin, clarithromycin, dirithromycin, roxithromycin, josamycin, kitasamycin, midecamycin, miocamycin, rokitamycin, rosaramicin, azithromycin and derivatives thereof, e.g. salts such as phosphates and esters such as acetates.

Azithromycin [(2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-(2,6-Dideoxy-3-C-3-O-dimethyl- $\alpha$ -L-ribohexopyranosyloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-(3,4,6-trideoxy-3-dimethylamino- $\beta$ -D-xylohexopyranosyloxy)-1-oxa-6-azacyclopentadecan-15-one], available commercially in the dihydrate form as Zithromycin®, is a preferred macrolide or azalide antibiotic for use in accordance with the invention, having proved effective using single daily dosages over periods as short as three days. It will be appreciated that such simple dosage regimens are highly advantageous in securing patient compliance.

periods as short as three days. It will be appreciated that such simple dosage regimens are highly advantageous in securing patient compliance.

A typical daily dose of a macrolide antibiotic such as azithromycin will be 500 mg given orally, for example for up to 3 days, although other dosages and methods of administration may if desired be employed. It may be advantageous to administer a second course of the antibiotics some time, e.g. one, two or three months, after the first course in order to maximise the effect of the treatment. It may be even more advantageous to administer further courses of the antibiotic at intervals of one, two or three months after the second course in order to sustain the benefit. Typically this may be carried out for up to a year after the initial course has been administered.

The invention will now be described in a non-limiting manner by way of example:

#### Example 1

A randomised double-blind study was conducted in which 60 male post-myocardial infarction patients were treated with azithromycin (500 mg per day, given orally for 3 days) or placebo. A further blinded course of azithromycin or placebo was given to 45 of the patients after a further 3 months. The results showed that azithromycin, particularly after double therapy, led to significant reduction in *Chlamydia pneumoniae* antibody titres (IgG) and to reduced levels of monocyte tissue factor, CD11b expression and serum markers of hypercoagulation and inflammation such as total leucocyte count and serum neopterin.

#### Example 2

The relationship between antibodies against anti-*Chlamydia pneumoniae* (Cp) and future cardiovascular events in male survivors of myocardial infarction (MI)

was explored. The effect of azithromycin antibiotic therapy was assessed in a subgroup of post-MI patients.

Between February 1995 and September 1995, 220 consecutive male patients attending a post-MI outpatient clinic at St George's Hospital, London were enrolled. Patients were screened for serum IgG antibodies against Cp by a microimmunofluorescence assay with elementary bodies of Cp strain IOL-207 as test antigen. Patients with chronic bronchitis, those currently taking macrolide antibiotics, and those with MI within the preceding 6 months (to ensure resolution of immune responses caused by infarction) were excluded. Also excluded were any subjects with serum that cross-reacted with *Chlamydia trachomatis* or *Chlamydia psitticai* antigens. Patients were stratified into one of three anti-Cp antibody titre groups: group Cp-ve (n=59), no detectable anti-Cp antibodies (seronegative); group Cp-I (n=74), seropositive at a serum dilution of between 1/8 and 1/32; and group Cp+ve (n=80), seropositive at a serum dilution of  $\geq 1/64$ . Anti-Cp antibody titres were remeasured after 3 months in the latter group. Patients with Cp titre ( $\geq 1$  in 64) on both occasions were entered in a double-blind placebo-controlled study of the effects of azithromycin therapy (either 500 mg/d for 3 days or two such courses 3 months apart) on anti-Cp titre and hemostatic and inflammatory markers in post-MI patients. These patients had their anti-Cp titre and other markers tested at 3 and at 6 months.

Adverse cardiovascular events (defined as the first admission to hospital with nonfatal MI; unstable angina requiring either intravenous anti-anginal therapy, coronary angioplasty, or urgent coronary artery bypass surgery; or cardiovascular death) were monitored for 18 months from the original Cp titre determination. The information was obtained from patients' clinic visits, telephone enquiries, case notes, and hospital computerised records.

### Statistical Analysis

The frequency of adverse events was assessed in groups Cp-ve, Cp-I and Cp+ve. Additionally, Cp+ve patients were further divided into three subgroups: Cp+ve-NR, patients who did not enter the antibiotic study; Cp+ve-P, patients who were randomized to receive placebo medication; and Cp+ve-A, patients who were given either a single or double course of azithromycin.

The proportion of patients experiencing an adverse event was compared between group Cp-ve and all other groups by use of the  $\chi^2$  test. The ORs for adverse cardiovascular events in each Cp+ve group relative to group Cp-ve were calculated by use of a multiple logistic regression model before and after adjustment for age, diabetes mellitus, hypertension, hyperlipidemia, smoking status (current, ever, or never) and previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (STATA analysis). A value of  $P < .05$  was considered significant.

### Results

Seven patients were excluded because their sera cross-reacted with other chlamydial species; analysis is hence based on the remaining 213 patients. Table 1 shows the baseline clinical characteristics. Patients with persisting seropositivity of  $\geq 1/64$  were randomized to either oral azithromycin (Cp+ve-A, 500 mg/d for 3 days [n=28] or 500 mg/d for 6 days [n=12]) or placebo (Cp+ve-P, n=20). Of the remaining 12 patients, 7 were unwilling to enter the trial, and 5 had other serious medical conditions that prevented their inclusion.



**Table 1 - Patient Characteristics and Incidence of Cardiovascular Events at a Mean of 18±4 Months of Follow-up**

Group	Cp-ve (n=59)	Cp-I (n=74)	Cp+ve-NR (n=20)	Cp+ve-P (n=20)	Cp+ve-A (n=40)
Age, y (mean±SD)	63±8	61±9	63±9	60±9	58±7
Diabetes mellitus, n(%)	6 (10)	9 (12)	6 (30)	8 (40)	12 (30)
Hypertension, n(%)	15 (25)	9 (12)	3 (15)	4 (20)	7 (18)
Previous PTCA or CABG, n(%)	12 (20)	20 (27)	8 (40)	6 (30)	12 (30)
Hyperlipidemia, n(%)	23 (39)	31 (42)	10 (50)	7 (35)	18 (45)
Smoking (past), n(%)	39 (66)	40 (54)	14 (70)	10 (50)	21 (53)
Smoking (current), n(%)	7 (12)	16 (22)	3 (15)	5 (25)	14 (35)
Months since MI, mean±SD	44±14	44±27	46±32	39±24	47±32
Anterior MI, %	53	53	50	58	53
Ejection fraction, %	41±14	45±13	41±19	47±14	48±14
Adverse cardiovascular events, n					
Death	0	0	1	1	1
Unstable angina/MI	0	7	4	4	2
PTCA/CABG	4	4	1	0	0
Total (%)	4 (7)	11 (15)	6 (30)	5 (25)	3 (8)
$\chi^2$ vs Cp-ve		2.1	7.3	4.9	0.9
P		.1	.007	.03	NS

Cp-ve indicates seronegative group of patients; Cp-I, group with intermediate antibody titres; Cp+ve-NR/P, group with elevated antibody titres either randomized to placebo or not randomized; Cp+ve-A, group with elevated antibody titres randomized to azithromycin; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass surgery.

At 6 months, in the patients participating in the antibiotic trial, anti-Cp titre fell to  $\leq 1/16$  in 43% of patients (17 of 40) receiving azithromycin compared with only 10% patients (2 of 20) taking placebo ( $P=.02$ ). The ORs for adverse cardiovascular events are shown for all groups in Table 2. The frequency of adverse events increased with rising anti-Cp titre, which persisted after correction for confounding variables. Because there were no significant differences in cardiovascular risk factors or events between the Cp+ve-NR and Cp+ve-P groups, results of the two groups were combined in the calculation of the ORs. The rate of further cardiovascular events in the Cp+ve-A group was similar to that in the Cp-ve group (8% versus 7%; OR, 0.9;  $P=NS$ ). Compared with patients in the combined placebo/nonrandomized group, the azithromycin-treated group had a fivefold reduction in cardiovascular events, with an OR of 0.2 (95% confidence interval, 0.05 to 0.8;  $P=.03$ ). There was no difference between the patients receiving either single or double azithromycin course in the proportion having a decrease in anti-Cp titre or the cardiovascular event rate.

**Table 2 - ORs for CV Events in Seronegative and Seropositive Patient Groups**

Group	Total CV Events, n(%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Cp-ve (n=59)	4 (7)		
Cp-I (n=74)	11 (15)	2.4 (0.7-8.0)	2.0 (0.6-6.8)
Cp+VE-NR/P (n=40)	11 (28)	5.2 (1.5-17.8) *	4.2 (1.2-15.5) †
Cp+ve-A (n=40)	3 (8)	1.1 (0.2-5.3)	0.9 (0.2-4.6)

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See Table 1 for explanation of group designations

Comparisons of cardiovascular (CV) events are for all groups relative to group Cp-ve (expressed as OR (95% confidence interval [CI])). Adjusted OR calculated after controlling for the following variables: age, diabetes mellitus, smoking status, hypertension, hyperlipidemia and previous coronary revascularization.

\*P=.008,

+.03 vs group Cp-ve.

CLAIMS

1. A method of combatting atherosclerosis, said method comprising administering an effective amount of azithromycin or a derivative thereof, optionally together with one or more pharmaceutically acceptable carriers or excipients, to a subject.
2. A method as claimed in claim 1 wherein a second effective amount of azithromycin is administered about one month after administration of a first effective amount of azithromycin.
3. A method as claimed in claim 2 wherein one or more further effective amounts of azithromycin are added at intervals of one month or more.
4. Use of azithromycin or a derivative thereof for the preparation of a medicament for use in combatting atherosclerosis.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 97/02862

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 22819 A (BOARD OF REGENTS OF THE UNIVERSITY OF WASHINGTON) 23 December 1992 see page 3, line 31 - line 35 see page 9, line 9 - line 34 see page 16, line 23 - line 28 see page 22 see page 25 lines 33-34, 37-39 ---	1-4
X	MARRIE: "Chlamydia pneumoniae" THORAX, vol. 48, no. 1, 1993, see page 2, right-hand column see page 3 --- -/-	1,4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

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\*Z\* document member of the same patent family

Date of the actual completion of the international search

19 February 1998

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Intern 1al Application No

PCT/GB 97/02862

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>COOK : "Chlamydia pneumoniae" J. ANTIMICROB. CHEMOTHER., vol. 34, no. 6, December 1994, pages 859-73, XP002056252 see page 865</p> <p style="text-align: center;">---</p>	1,4
X	<p>COOK: "Clinical aspects of Chlamydia pneumoniae infection" PRESSE MED. (FR.), vol. 24, no. 5, 4 February 1995, pages 278-282, XP002056253 see page 280, right-hand column see page 281</p> <p style="text-align: center;">---</p>	1,4
X	<p>VALTONEN: "Symposium graft infection sponsored by the Sanofi-Chinoïn Co: the causative role of Chlamydia pneumoniae and other bacteria in the development of coronary heart disease" INT. ANGIOLOGY, vol. 15, no. 2sup1, May 1996, page 61 XP002056254 abstract nr 034.</p> <p style="text-align: center;">---</p>	1,4
X	<p>BLANCHARD: "Chlamydia infections" BR. J. CLIN. PRACT., vol. 48, no. 4, 1994, pages 201-205, XP002056255 see page 202; table 1 see page 203, left-hand column see page 204, left-hand column</p> <p style="text-align: center;">---</p>	1,4
X	<p>GAYDOS: "Chlamydia pneumoniae: a review and evidence for a role in coronary artery disease" CLIN. MICROBIOL. NEWSLETTER, vol. 17, no. 7, 1995, pages 49-54, XP002056256 see page 51</p> <p style="text-align: center;">---</p>	1,4
P,X	<p>STILLE: "Argumente für eine Antibiotika-Therapie der Atherosklerose" CHEMOTHER. J., vol. 6, no. 1, 21 April 1997, pages 1-5, XP002056257 see the whole document</p> <p style="text-align: center;">-----</p>	1,4

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 97/ 02862

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-3  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 1-3 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

### Information on patent family members

Internal Application No	Internal Application No
1	1
2	2
3	3
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11	11
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PCT/GB 97/02862

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WO 9222819 A	23-12-92	AU 2249892 A	12-01-93
		US 5424187 A	13-06-95
		ZA 9206713 A	09-03-93
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<p>(21) International Application Number: PCT/GB97/02862</p> <p>(22) International Filing Date: 17 October 1997 (17.10.97)</p> <p>(30) Priority Data:</p> <table border="0"><tr><td>9621771.6</td><td>18 October 1996 (18.10.96)</td><td>GB</td></tr><tr><td>028,693</td><td>18 October 1996 (18.10.96)</td><td>US</td></tr></table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</p> <table border="0"><tr><td>US</td><td>028,693 (CIP)</td></tr><tr><td>Filed on</td><td>18 October 1996 (18.10.96)</td></tr></table> <p>(71) Applicant (for all designated States except US): ST. GEORGE'S ENTERPRISES LTD. [GB/GB]; St. George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE (GB).</p> <p>(72) Inventor; and</p> <p>(75) Inventor/Applicant (for US only): GUPTA, Sandeep [GB/GB]; 26 Broomfield Avenue, Palmers Green, London N13 4JN (GB).</p> <p>(74) Agents: MARSDEN, John, Christopher et al.; Frank B. Dehn &amp; Co., 179 Queen Victoria Street, London EC4V 4EL (GB).</p>		9621771.6	18 October 1996 (18.10.96)	GB	028,693	18 October 1996 (18.10.96)	US	US	028,693 (CIP)	Filed on	18 October 1996 (18.10.96)	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b></p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: METHOD OF TREATMENT OF HEART DISEASE CAUSED BY CHLAMYDIA PNEUMONIAE</p> <p>(57) Abstract</p> <p>A method of combatting atherosclerosis, said method comprising administering an effective amount of a macrolide antibiotic, for example an azalide such as azithromycin, optionally together with one or more pharmaceutically acceptable carriers or excipients, to a subject.</p>												

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